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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,991	03/15/2006	Laurent Francois Andre Hennequin	09963.0008	5523

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EXAMINER	
WILLIS, DOUGLAS M	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
12/30/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/571,991	HENNEQUIN ET AL.	
	Examiner	Art Unit	
	DOUGLAS M. WILLIS	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *38-43* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *38-43* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06-16-11; 09-15-11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

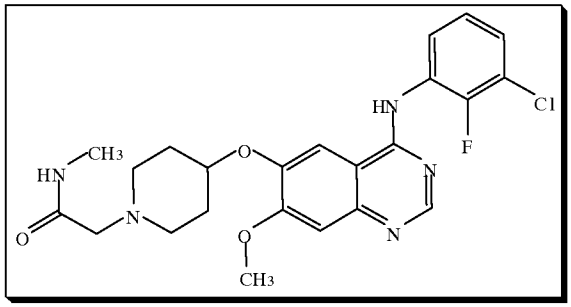
Status of the Claims / Priority

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the *Final Rejection*, mailed on March 16, 2011, has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission, filed on September 15, 2011, has been entered.

Claims 38-43 are pending in the current application. According to the *Amendments to the Claims*, filed April 6, 2009, claims 39, 40, 42 and 43 were amended and claims 1-37 and 44-71 were cancelled. This application is a 35 U.S.C. § 371 National Stage Filing of International Application No. PCT/GB2004/03937, filed September 15, 2004, which claims priority under 35 U.S.C. § 119(a-d) to: a) EP 04291248.5, filed May 14, 2004; and b) EP 03292309.6.7, filed September 19, 2003.

Status of Restrictions / Election of Species

Applicant's affirmation of the following election, without traverse, in the reply filed on December 11, 2008, is acknowledged: a) Group I, claims 38-43; and b) substituted quinazolinamine - p. 58, example 1, shown to the left, and hereafter referred to as 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline.



The requirement was made FINAL in the *Final Rejection*, mailed on January 6, 2009.

The sections of U.S.C. Title 35 that formed the basis of prior rejections formulated, as well as any references supporting said rejections, that are not included with this Office action, may be found in either the *Non-Final Rejection*, mailed on August 19, 2008, the *Final Rejection*, mailed on January 6, 2009, the *Non-Final Rejection*, mailed on May 26, 2009, the *Final Rejection*, mailed on November 27, 2009, the *Final Rejection*, mailed on August 26, 2010, or the *Final Rejection*, mailed on March 16, 2011. Furthermore, any rejections and/or objections of record not explicitly addressed herein below, are hereby withdrawn, in light of applicant's arguments, filed September 15, 2011, and/or the *Amendments to the Claims*, filed April 6, 2009.

Thus, a seventh Office action and prosecution on the merits of claims 38-43 is contained within.

Status of Claim Rejections - 35 U.S.C. § 103

Applicant's arguments, on pages 2-10 of the *Remarks*, filed September 15, 2011, with respect to claims 38-43, have been fully considered, but are not persuasive. Consequently, the rejection of claims 38-43, made in the *Final Rejection*, mailed on March 16, 2011, is hereby maintained for the reasons of record.

Applicant primarily argues that the examiner has engaged in a blatant *hindsight* analysis, which directly contradicts the MPEP, the USPTO's own Examination Guidelines and controlling precedent for stating a *prima facie* case of obviousness based on structural similarity. Furthermore, applicant further argues that (1) the Office has failed to make a reasoned identification of a *lead* compound, and that (2) the Office has failed to identify a reason to make the requisite modification to example 38.

In response to applicant's arguments that the examiner has engaged in a blatant *hindsight* analysis, which directly contradicts the MPEP, the USPTO's own Examination Guidelines and controlling precedent for stating a *prima facie* case of obviousness based on structural similarity, the examiner respectfully disagrees, since, *it must be recognized that any judgment on obviousness is, in a sense, necessarily a reconstruction based upon hindsight reasoning. Provided it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and excludes knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.* {See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971)}.

Similarly, in response to applicant's arguments that the Office has failed to make a reasoned identification of a *lead* compound, the examiner respectfully disagrees, since, in keeping with the flexible nature of the inquiry of obviousness after *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 [82 USPQ2d 1385] (2007), the motivation to select and modify a *lead*__ compound__ need not be explicit in the art. {See *Eisai*, 533 F.3d at 1357; and *Takeda*, 492 F.3d at 1356-57}.

Likewise, MPEP § 2144-I states that *the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law.* {See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir.

1990); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)}.

Moreover, in response to applicant's arguments that the Office has failed to identify a reason to make the requisite modification to example 38, the examiner further respectfully disagrees, since, the *Daiichi Sankyo Co. v. Matrix Laboratories Ltd.* decision differs considerably in its facts from the facts presented herein.

In *Daiichi Sankyo Co. v. Matrix Laboratories Ltd.*, the facts led to a finding that medicinal chemists of ordinary skill in the art would not have been motivated to modify the prior-art angiotensin receptor blocker (ARB) compounds, employed as *lead*__ compounds by the inventors of the patent in suit, to obtain olmesartan medoxomil claimed in the allegedly infringed patent for antihypertensive drugs, since, the compounds in the prior art clearly favored use of lipophilic groups as substituents at the 4-position of the imidazole ring, as *lead*__ compounds, rather than the hydrophilic group of olmesartan medoxomil. Furthermore, the analysis of regioisomer pairs, wherein 4- and 5-positions are transposed, and certain second-generation angiotensin receptor blocker (ARB) compounds, confirmed preference for lipophilicity at the 4-position of the imidazole ring. Consequently, based upon the prior art structural-activity relationship (SAR) data and the structure of second-generation angiotensin receptor blocker (ARB) compounds, it was concluded that a person of skill in the art would not have been motivated to modify the lead__ compounds' lipophilic alkyl groups to the hydrophilic group of olmesartan medoxomil, since, one example from the prior art patent showing a hydrophilic hydroxymethyl group at the 4-position does not provide adequate

motivation to modify lead__ compounds due to SAR data in that patent contradicting any such conclusion, and since one of ordinary skill would not select lead__ compounds with increased lipophilicity at the 4-position only to disregard that distinguishing characteristic. Finally, even if it were assumed that the prior patent failed to *teach away* from a hydrophilic group at the 4-position, the patent fails to provide reason to make such a modification.

In the instant case, it is the examiner's position that applicant is confusing *negative* or *undesirable* properties, which existed for the reference compound in *Daiichi Sankyo Co. v. Matrix Laboratories Ltd.*, with *different* properties, which applicant urges exist for its compound in comparison to the prior art reference compound.

Furthermore, to-date, there is no convincing evidence of record to suggest that the proposed modification to the *4-(3-chloro-**4-fluoro**anilino)* regioisomer of reference example 38 would have a deleterious effect on its antitumor activity. Thus, it is the examiner's position that the prior art of record lacks a requisite *teach away* aspect.

Applicant should direct their attention to MPEP § 2141.02-VI, which not only relates to references that may *teach away*, but also states that alternative embodiments should **not** be confused with *teaching away*. See *In re Fulton* at 73 USPQ2d 1141.

Similarly, applicant should further note that under the Patent Act, *[a] patent may not be obtained... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.*" See 35 U.S.C. § 103(a).

In *Daiichi Sankyo Co. v. Matrix Laboratories Ltd.*, based on a preponderance of the

evidence presented, a decision was rendered wherein the prior art reference compound, which possessed inferior potency as well as other unfavorable biological properties (i.e. *lipophilicity*), was disqualified based on *unexpected results* and *a reasonable expectation of success* in performing the intended use.

Finally, applicant should note that a *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. {See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); *In re Wiechert*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967); and *In re Peterson,* 65 USPQ2d 1379 (Fed. Cir. 2003)}.

As a result of the *Amendments to the Claims*, filed April 6, 2009, and to clarify the record, the rejection, made in the *Final Rejection*, mailed on March 16, 2011, is included below, in the section entitled *New Claim Rejections - 35 U.S.C. § 103*.

New Claim Rejections - 35 U.S.C. § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

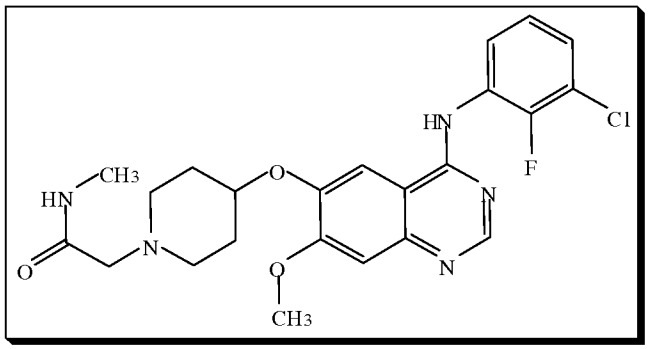
The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

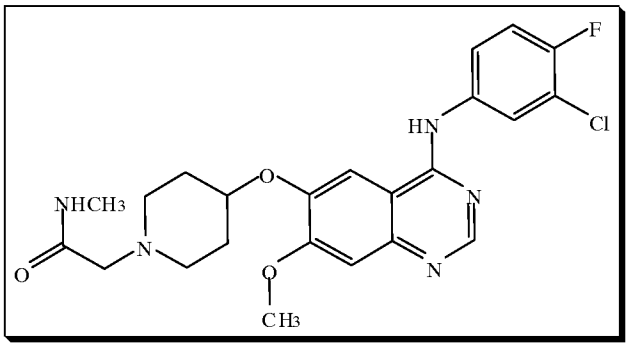
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 38-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Himmelsbach, et al. in US 6,924,285.

The instant application recites 4-(3-chloro-**2-fluoro**anilino)-7-methoxy-6-{[1-(*N*-methyl-carbamoylmethyl)piperidin-4-yl]oxy}-quinazoline, shown to the left, and a pharmaceutically acceptable salt or pharmaceutical composition thereof, as an anti-tumor agent.



Himmelsbach, et al. (US 6,924,285), as cited on the IDS and in the *Final Rejection*, mailed on March 16, 2011, teaches 4-(3-chloro-**4-fluoro**anilino)-7-methoxy-6-{[1-(*N*-methylcarbamoyl-methyl)piperidin-4-yl]oxy}-quinazoline, shown to the right, and a physiologically acceptable salt or pharmaceutical composition thereof, as a therapeutic agent for treating tumoral diseases [columns 69 and 70, compound 38; physiologically acceptable salts - column 18, lines 41-48; and pharmaceutical compositions - column 1, lines 17-18]. Moreover, in the genus disclosure, Himmelsbach discloses that *p*-fluoro and *o*-fluoro are alternatively usable on the anilino ring at C-4 of the quinazoline core [R^b: column 1, lines 53-54; and R^1-R^3: column 1, line 56 - column 2, line 3].



The only difference between the instantly recited 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(*N*-methyl-carbamoylmethyl)piperidin-4-yl]oxy}quinazoline and Himmelsbach's 4-

(3-chloro-4-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}-quinazoline is the instantly recited 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline has an *o*-F on the anilino ring at C-4 of the quinazoline core, whereas Himmelsbach's 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline has a *p*-F on the anilino ring at C-4 of the quinazoline core.

In the chemical arts, it is widely accepted that *structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions or compounds, creates a prima facie case of obviousness*. {See *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, No. 06-1329, slip op. at 9 (Fed. Cir. June 28, 2007) (quoting *In re Dillon*, 919 F.2d 688, 692 [16 USPQ2d 1897] (Fed. Cir. 1990) (en banc)); and *In re Papesch*, 315 F.2d 381]137 USPQ 43] (C.C.P.A. 1963)}.

Consequently, since: a) Himmelsbach teaches 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, where *p*-F is bonded to the anilino ring at C-4 of the quinazoline core; b) Himmelsbach teaches that 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline and 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline are alternatively usable; and c) the courts have recognized that *structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions or compounds, creates a prima facie case of obviousness*, one having ordinary skill in the art, at the time this

invention was made, would have been motivated to utilize the teachings of Himmelsbach and replace the *p*-F of the anilino ring at C-4 of the quinazoline core in Himmelsbach's 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline with an alternatively usable *o*-F, and formulate a pharmaceutically acceptable salt or pharmaceutical composition thereof, with a reasonable expectation of success and similar therapeutic activity, rendering claims 38-43 obvious.

Although not explicitly discussed herein, applicant is advised to note that the Himmelsbach reference contains additional species that may obviate the instantly recited 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline. Consequently, any amendments to the claims and/or arguments formulated to overcome rejections rendered under 35 U.S.C. § 103(a) should address this reference as a whole and should not be limited to the species discussed or disclosed explicitly herein.

Finally, this application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Allowable Subject Matter

No claims are allowed.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114.

Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DOUGLAS M. WILLIS, whose telephone number is 571-270-5757. The examiner can normally be reached on Monday thru Thursday from 8:00-6:00 EST. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Mr. James O. Wilson, can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DOUGLAS M WILLIS/
Examiner, Art Unit 1624

/JAMES O. WILSON/
Supervisory Patent Examiner, Art Unit 1624